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Possible Role of Natural Killer Cells and Other Effector Cells in Immune Surveillance Against Cancer

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The concept of immune surveillance against cancer was initially formulated with thymus-dependent immunity as a central and requisite effector mechanism. However, a substantial amount of evidence has accumulated to indicate that T cell-mediated immunity is mainly important for protection against tumors induced by oncogenic viruses and not for many other types of spontaneous or chemical carcinogen-induced tumors. It now appears likely that various components of the natural immune system also play major roles in immune surveillance. These include natural killer (NK) cells and macrophages. The existing evidence for the roles of these effector cells is discussed.

The general role of the immune system in preventing or limiting tumor growth has been proposed by many investigators. The central concept, which has come to be known as the *immune surveillance hypothesis*, postulates that the immune system plays a central role in resistance against the development of detectable tumors. The first known suggestion along these lines came from Paul Ehrlich in 1909 [1]. The modern formulation of the hypothesis originated from Burnet [2] and Thomas [3]. When information about thymus-dependent immunity became known, and particularly when T cells were found to play a central role in homograft rejection, the immune surveillance hypothesis was modified by Burnet to stress the key role of this effector mechanism in antitumor resistance [4].

Since these original formulations, the immune surveillance hypothesis has generated many experimental studies and much discussion and controversy. One of the reasons for the controversy is that the concept leads to a series of predictions, and most available evidence relates to tests of one or more of the following predictions: (1) tumor cells have transplantation-type antigens, (2) resistance against tumors is T cell-dependent and analogous to the homograft reaction, (3) there is a close evolutionary link between malignancy and the development of an immune system with a capability for rejection of tumors, (4) immune depression is associated with, and must precede, development of detectable tumors, and (5) a requisite action of carcinogens and/or tumor promoters might be immunosuppression.

The main support for the immune surveillance hypothesis has come from evidence related to prediction 4, since naturally occurring or induced immunodepression has been associated with a higher incidence of some types of tumors. In experimental tumors, this has been most clearly demonstrated with those induced by oncogenic viruses. Neonatal thymectomy and other forms of immune suppression have been shown to lead to increased susceptibility to polyoma virus-induced tumors in mice [5] and Marek's disease in chickens [6]. There is also considerable clinical evidence that immune deficiency diseases are associated with a much higher incidence of lymphomas and leukemias [7]. Allograft recipients receiving immunosuppressive agents, mainly prednisone and azathioprine, have also been found to have an increased incidence (approximately 100-fold increase) of tumors [8]. Patients with cancer, arthritis, or other diseases who received chemotherapeutic (mainly alkylating) agents have been subsequently found to develop a relatively high frequency of primary malignancies, mainly leukemias and lymphomas [9]. The recent observations of a remarkably high incidence of Kaposi's sarcoma in young adults with the acquired immune deficiency syndrome are yet another indication of the association of malignancy with immunodepression.

Although such data have lent considerable support to the immune surveillance hypothesis, several major problems or limitations of the original hypothesis were noted. First, the majority of human tumors associated with immunodepression have been leukemias and lymphomas, rather than a complete array of the common types of malignancy. Second, there has been a lack of a consistent association between immunodepression and tumors [10]. Third, neonatally thymectomized mice have been found to have a decreased incidence of mammary tumors [11], and nude and euthymic mice have similar incidences of spontaneous and carcinogen-induced tumors [10]. Fourth, most spontaneous tumors of experimental animals lack detectable tumor-associated transplantation antigens [12]. Finally, there has also appeared to be an evolutionary dissociation between the development of tumors and the appearance of a sophisticated immune system and T cells [13].

These hypotheses have led to the suggestion [14] that immune surveillance may be operative only against tumors induced by oncogenic viruses, which have strong transplantation antigens and for which immune T cells have been shown to be important in resistance. Other investigators have reacted to such information in a more pessimistic way. For example, Nossal [15] suggested that immune surveillance and tumor immunology in general were moribund if not terminally ill. The major exceptions to the central role of immune T cells in resistance to tumor growth have even led to a countertheory of immunostimulation [16], suggesting that the immune system may have mainly enhancing effects on tumor induction and growth.

A more likely explanation for many of the discordant results is that a variety of effector mechanisms may be involved in host resistance. In the last few years it has become apparent that natural immuniity, as well as specifically induced immune responses, may contribute to host defenses. When T cell-mediated immunity is viewed as only one of a series of possible host defense mechanisms, the evidence summarized above need not be viewed in such a negative light. Target cell structures other than tumor-associated transplantation antigens might be involved in recognition by other types of effector cells, and in T cell-deficient individuals, natural immunity might still be functional and capable of resisting tumor growth.

POSSIBLE EFFECTORS OF IMMUNE SURVEILLANCE

Possible Role of T Cells in Immune Surveillance

As indicated above, there is substantial evidence that thymus-dependent immune responses play a central role in resist-

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Abbreviations:
ADCC: antibody-dependent cellular cytotoxicity
LGL: large granular lymphocytes
NC cells: natural cytotoxic cells
NK cells: natural killer cells

ance to tumors induced by oncogenic viruses. However, the absence of the thymus has not been associated with increased susceptibility to other types of tumors, suggesting a limited role for T-cell immunity in immune surveillance. Further, the inability to detect tumor-associated transplantation antigens on most spontaneous rodent tumors argues against a major involvement of specific immune responses.

What then are the likely alternatives to T cell-mediated immunity in antitumor resistance and immune surveillance? There are a variety of possibilities, including macrophages, natural killer (NK) cells, natural cytotoxic (NC) cells and other components of the natural immune system, granulocytes, and antibody-dependent cellular cytotoxicity (ADCC) with natural or induced antibodies. Based on these possibilities, one may formulate an updated immune surveillance hypothesis: Transformed cells express surface antigens or other structures that can be recognized by one or more components of the immune system. One or more components of the natural and/or induced immunologic effector mechanisms can eliminate the transformed cells or impede the progression and spread of tumors.

This broader hypothesis leads to a somewhat different set of predictions: First, tumor cells have surface structures recognized by one or more effectors. Second, tumor cells will be susceptible to lysis or growth inhibition by one or more effector mechanisms. Third, one or more of the relevant effector cells should be able to enter the site of tumor growth. Fourth, augmentation of relevant effector mechanism(s) will decrease the incidence of tumors or of metastases. Fifth, depression of relevant effector mechanism(s), either by carcinogen or by immunosuppressive treatment, will increase the incidence of tumors or metastases. Finally, restoration of depressed effector activity will decrease the incidence of tumors or metastases.

Possible Role of Macrophages in Immune Surveillance

Many investigators have suggested that macrophages might play an important role in antitumor defenses and might be primarily responsible for immune surveillance against tumors [17,18], and this possibility is supported by several lines of evidence: First, there is abundant evidence that macrophages can accumulate in considerable numbers in a variety of transplantable tumors [19] and in many primary tumors [20]. Second, macrophages have natural [21] as well as the rapidly activatable ability to lyse or inhibit the growth in vitro of a wide variety of transformed cells. Third, several treatments that can depress the function of macrophages (e.g., silica or carrageenan) have been associated with an increased incidence of tumors and metastases [22]. Fourth, adoptive transfer of in vitro or in vivo activated macrophages was shown to inhibit the metastatic spread of some tumor cell lines [23,24]. Fifth, some carcinogens (e.g., methylcholanthrene and acetylaminofluorene) have been shown to depress reticuloendothelial function [25]. Finally, stimulation of macrophage function by various immunomodulators has been associated with decreased tumor growth or a decreased incidence of tumors [22].

It should be noted that there are some major limitations to such evidence: First, there is remarkably little evidence that macrophages have cytotoxic activity against primary, freshly harvested tumor cells, as opposed to established tumor cell lines. Second, silica and carrageenan, and virtually all the other depressive treatments that have been used, may not be entirely selective in their effects. In fact, they may cause increases in some functions, particularly suppressor activity, by macrophages or other cells [26]. Further, the effects of such treatments on tumor growth are not always in the same direction, even with the same tumor. For example, Mantovani et al [27] found that treatment of mice with silica or carrageenan increased the incidence of pulmonary metastases but inhibited the growth of the primary tumors. Third, the carcinogens shown to depress reticuloendothelial function may also have affected a variety of effector mechanisms, and other carcinogens have had no detectable effects on macrophage or reticuloendothelial function [28].

Possible Role of NK Cells in Immune Surveillance

Natural killer (NK) cells have come to be recognized as a discrete subpopulation of lymphoid cells with spontaneous cytotoxic reactivity against a variety of tumor cell lines and primary tumor cells, as well as against virus-infected cells and some normal cells (for a comprehensive compendium of recent information on the charactertistics of NK cells, see [29]). NK cells are readily distinguishable by their cell surface phenotype and by their pattern of specificity (particularly the lack of major histocompatibility complex restriction to their activity) from classical cytotoxic T cells. They are also nonphagocytic and generally nonadherent and thus distinguished from typical macrophages, monocytes, and granulocytes. It has recently become clear that a small, morphologically identifiable subpopulation of lymphoid cells, termed *large granular lymphocytes* (LGL), accounts for virtually all NK activity in humans and rats, and this close association also seems to pertain to mouse NK cells. LGL, which represent 5–10% of the mononuclear cells in the peripheral blood or spleen, can be enriched to as much as 90% purity, primarily by centrifugation on discontinuous gradients of Percoll. The ability to prepare highly enriched populations of NK cells has allowed extensive characterization of the cell surface phenotype of NK cells. In general, they have been shown to express some markers that have been associated with T cells or with macrophages or granulocytes.

There is substantial evidence for an important role of NK cells in in vivo resistance against established cell lines of tumors, particularly those which show susceptibility to in vitro cytolysis by NK cells (summarized in [30]). In addition, there are several types of evidence that conform to the predictions of the immune surveillance hypothesis: First, NK cells have been shown to be able to accumulate at sites of inflammation [31] and in small primary as well as transplanted tumors [32]. Second, NK cells have a natural and also rapidly activatable ability to lyse a variety of primary autochthonous tumors [33, 34]. Third, there is considerable evidence for the ability of NK cells to eliminate metastatic tumor cells and thereby resist tumor spread. Fourth, an increased tumor incidence (primarily lymphomas) has been found in individuals with depressed NK activity (beige mice [35], patients with Chediak-Higashi syndrome [36], and immunosuppressed transplant recipients [8]). Some carcinogens (urethane, γ- or x-irradiation, and dimethylbenzanthracene) have been shown to cause early, profound depression of NK activity [37–40].

The most convincing data relate to the important role of NK cells in host resistance against metastases. The observation that NK cells appear to be mainly responsible for the rapid elimination of intravenously inoculated tumor cells provided the initial indication that this effector mechanism might provide a very effective control of hematogenous spread of tumors [41]. Experimental support for this possibility first came from the finding that cells from the lung metastases of a transplantable tumor in mice were more resistant to NK activity than locally growing tumor cells [42]. An important role of NK cells in resistance against metastatic growth of transplantable tumors has been further supported by observations that suppression or augmentation of NK activity of mice was associated with parallel alterations in resistance to artificial metastases produced by intravenous inoculation of tumor cells [43,44]. The patterns of results obtained in these studies suggested that NK cells may primarily influence metastatic spread of tumors by acting during the phase of hematogenous dissemination, presumably by their ability to rapidly eliminate the tumor cells from the circulation of capillary beds. As further confirmation of the association between depressed NK activity and increased metastases, Barlozzari et al (manuscript in preparation) have shown that selective restoration of NK activity in rats by

adoptive transfer of highly purified large granular lymphocytes was accompanied by increased resistance to pulmonary metastases. Similarly, Warner and Dennert [45] showed that adoptive transfer of a clone of cultured lymphoid cells with NK-like activity protected against development of pulmonary or liver metastases.

Direct evidence for a possible role of NK cells in immune surveillance is quite limited and relates mainly to two models of carcinogenesis: First, there are several indications for a role of NK cells in protection against urethane-induced lung tumors in mice. This carcinogen produces lung tumors in only some strains of mice and was shown to cause transient and marked depression of NK activity in a susceptible strain [37] but not in resistant strains [46]. However, it is clear that genetically determined susceptibility to depression of NK activity by urethane is only one of the factors determining the strain distribution. C57BL/6 beige mice, with deficient NK activity, as well as normal C57BL/6 mice, were found to be highly resistant to urethane-induced lung tumors [47]. The resistance to lung carcinogenesis, even in the NK-deficient strain, is probably attributable to the known genetic resistance of the lung tissues of C57BL mice to transformation by urethane [48]. In further studies in A/J mice, which are highly susceptible to induction of lung tumors by urethane, a further reduction in NK activity by treatment with cyclophosphamide led to a significantly higher tumor incidence [47]. Conversely, adoptive transfer of normal spleen or bone marrow cells, which led to reconstitution of NK activity, also caused a significant inhibition in the subsequent incidence of lung tumors. In contrast, spleen cells from urethane-treated donors, which had low NK activity and were unable to restore NK activity in the recipients, had no significant ability to transfer resistance to development of lung tumors [47].

The other carcinogenesis system that has received considerable attention is the induction of thymic lymphomas by multiple low doses of γ-irradiation of C57BL/6 mice. Development of tumors in this system appears to be dependent on a complex series of factors, and it has been difficult to demonstrate a clear contribution of NK cells to the overall process of leukemogenesis [56]. However, NK cells did appear to be involved in protection against the transplantation of preleukemic bone marrow cells from donors that received fractionated doses of γ-irradiation. Recipients of the preleukemic bone marrow that were irradiated with 400 R were susceptible to leukemia and in parallel were found to have depressed NK activity. Whereas unirradiated C57BL/6 recipients were resistant, unirradiated C57BL/6 beige recipients were found to be susceptible to induction of leukemia by the transferred bone marrow cells. As further evidence for the possible role of NK cells in this transplantation system, spleen cells of nude mice, which have high NK activity, protected against the transfer of leukemia, whereas spleen cells from mice with low NK activity did not protect. Further positive evidence for a role of NK cells in resistance against leukemogenesis has come from the studies of Warner and Dennert [45]. They found that adoptive transfer of cloned cells with NK-like activity, during a 4-week period after the last dose of fractionated γ-irradiation, conferred substantial protection against the development of leukemia. Despite such suggestive positive evidence for a role of NK cells, a series [56] of other experiments has indicated that non-NK-related factors seemed to have a more important influence on the incidence of leukemia than did the levels of NK activity.

Possible Role of NC Cells in Immune Surveillance

As reviewed by Stutman et al [49], natural cytotoxic (NC) cells are another type of natural effector cell in mice that may be related to NK cells but lack some of the markers associated with NK cells and differ in some functional characteristics. Although some evidence has been obtained for an in vivo role of NC cells in resistance to tumor growth, to date little direct evidence has been accumulated to support a role of NC cells in immune surveillance.

Potentially Important Collaborations Between Different Effector Mechanisms

It is important to note that more than one effector mechanism may be involved in protection against development of a particular type of tumor. In addition to possible separate contributions by two or more effector mechanisms, in many instances the activity of a particular effector mechanism may be dependent on the activation or other form of collaboration from another component of the immune system. The best known example of such a collaboration is antibody-dependent cellular cytotoxicity (ADCC), in which natural or induced antibodies cooperate with effector cells. In addition to the well-known cytokine production by macrophages and by T cells, NK cells have been shown [50–53] to secrete a variety of cytokines (interferons, IL-1, IL-2, CSF, BCGF), and this function might contribute to the role of NK cells in resistance to tumors. It is also of note that lymphotoxin has been shown to have some anticarcinogenic activities in vitro and possibly also in vivo [54], and lymphotoxin-treated tumor cells had increased susceptibility to lysis by NK cells [55].

Another aspect to consider with regard to the possible involvement of multiple effector cells is the possibility of sequential contributions by natural effector cells and immune T cells. Because of their spontaneous levels of reactivity and/or their ability to be rapidly activated, NK cells and macrophages might be viewed as a first line of defense against small numbers of transformed cells. If these natural effector cells are not completely effective in eliminating the tumor cells, immune T-cell reactivity might be induced and be responsible for the subsequent elimination of tumor cells.

CONCLUSIONS

In the context of the updated, broad formulation of the hypothesis, immune surveillance does appear to exist, at least for certain types of experimental and human tumors. This conclusion is based primarily on the considerable evidence that various forms of immunodepression have been associated with an increased incidence of tumors. A major challenge to tumor immunologists is to determine the possible effector mechanism(s) involved in immune surveillance. This task will undoubtedly continue to be quite difficult, despite further studies along the lines outlined above. One problem is that most augmenting and suppressive treatments are not entirely selective for one effector mechanism. Furthermore, the lack of effect of a selective treatment on tumor incidence might be attributable to compensatory protection from an alternative effector mechanism. Conversely, a positive effect of a selective suppressive treatment on tumor incidence might only reflect cooperative involvement of that effector mechanism, with a different mechanism actually being the effector of resistance.

With such limitations in mind, what conclusions can be drawn from the available evidence as to the effector mechanisms responsible for immune surveillance? First, a critical role for T cells appears limited to tumors with strong tumor-associated transplantation antigens, particularly virus-induced tumors. Second, NK cells appear to contribute to antitumor resistance, especially against metastases; however, the available data are limited to very few carcinogenesis systems. Third, insufficient data are available to draw satisfactory conclusions regarding the extent of involvement of other effector mechanisms.

With regard to the potential of immunomodulation for prophylaxis or therapy of cancer, the questions of the overall efficacy of immune surveillance, or of the most relevant effector mechanisms in such resistance, are of secondary importance. Although natural host defenses may be inadequate to protect against tumor growth because of insufficiently low levels of

reactivity, augmentation of one or more effector mechanisms may inhibit and even abrogate malignant development. More studies focused on this important, practical issue are required.

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